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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,556	05/23/2001	Yoshiaki Azuma	TEI-120	9893

7590 08/26/2003

Rader Fishman & Grauer
Suite 501
1233 20th Street NW
Washington, DC 20036

EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	9

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/856,556	AZUMA ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed 06/20/03 (Paper No. 7), is acknowledged.

Claims 1-8 are pending.

Applicant's election of Group II, claims 1-8 and osteoclast forming factor as species of inducing factors in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Because of the amendment filed 06/20/03 (Paper No. 7), the restriction requirement set forth in Paper No:5 is moot.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is improper to recite " derivatives" in claims 6 and 8, both in line 7, because said claims can read on a mixture of derivatives that are used for the method for inhibiting bone resorption. However, claims 6 and 8 recited the method for inhibiting bone resorption, comprising using one factor. It is suggested that said word be changed to "derivative".

4 . The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection.**

"A method for inhibiting bone resorption by inhibiting osteoclast formation" claimed in Claim 1-8 represents a departure from the specification and the claims as originally filed and applicant has not pointed out where the support comes from. The specification and the claims as originally field only support "a method for inhibiting osteoclast formation or a method for inhibiting bone resorption".

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting osteoclast formation *in vitro*, comprising exposing cells to ultrasound conditions , wherein said conditions are disclosed in overlapping pages 5-6 of the Specification as field, does not reasonably provide enablement a method for inhibiting bone resorption *in vivo*, comprising exposing cells to *any* ultrasound conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses *in vitro* studies , wherein mouse bone-marrow derived osteoclast precursors (MDBM) were incubated in the presence of soluble osteoclast forming factor (sRANKL) and exposed to ultrasound that results in reduction of the numbers of osteoclasts (see Examples 1-2 in particular). However, said reduction was less than 10-15 % (as shown in Figures I and II) compare to untreated cells and specification does not adequately teach that said reduction would be sufficient to inhibit bone resorption *in vivo*. Moreover, the Specification disclosed that not *any* ultrasound condition, but very s pecific one as disclosed on overlapping pages 5-6 should be used (see Page 5-6 of the Specification as field). Luiz. R (US

Patent 4,530,360) also teaches that for most effective treatment with ultrasound a specific ultrasound conditions must be maintained (see entire document, column 2, lines 5-25 in particular). The specification does not adequately teach how to effectively inhibit bone resorption *in vivo*, comprising exposing cells to *any* ultrasound conditions. Moreover, no animals were used as model system to effectively inhibit bone resorption in a subject, comprising exposing cells to *any* ultrasound conditions. Since there is no animal model system in the specification to effectively inhibit bone resorption *in vivo*, comprising exposing cells to *any* ultrasound conditions it is unpredictable how to correlate *in vitro* results with *in vivo* use. Murrills R (IDS) teaches that *in vitro* bone resorption assays may not necessarily respon to some agents as adult tissue dould and the results from animal tissue may not necessary hold true for human tissues. In addition, these in vitro assays may not be representative of the long-term changes in bone metabolism (see entire document, page 1239 in particular). In addition, Bals R., et al., (Infection and Immunity, 1999, v.67, pages 6084-6089) teach that functional studies have been restricted primarily to *in vitro* experiments with purified peptides and do not necessarily reflect the complexity of *in vivo* interaction, such as synergism and antagonism between individual substances (see overlapping pages 6087-6088 in particular). Since the method for inhibiting bone resorption *in vivo*, comprising exposing cells to *any* ultrasound conditions can be species- and model-dependent, it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of inhibiting bone resorption *in vivo*, comprising exposing cells to *any* ultrasound conditions. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of a method for inhibiting bone resorption *in vivo*, comprising exposing cells to *any* ultrasound conditions are fraught with uncertainties.

Moreover, an effective protocol for a method of inhibiting bone resorption *in vivo*, is subject to a number of factors which enter the picture beyond simply exposing cells to *any* ultrasound conditions. Demonstrating *in vitro* that MDBM) when incubated in the presence of soluble osteoclast forming factor (sRANKL) and exposed to ultrasound results in reduction of the numbers of osteoclasts cannot alone support the predictability of a method inhibiting bone resorption *in vivo*. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

The specification does not provide sufficient teaching as to how it can be assessed that inhibition bone resorption in vivo was achieved after exposing cells to any ultrasound conditions. Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed

method for inhibiting bone resorption *in vivo* comprising exposing cells to any ultrasound conditions in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. No claim is allowed.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. For example, on page 15, line 8, the word "which" is misspelled. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
August 25, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600